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(71) Applicant (for all designated States except US): **PHARMACIA AB** [SE/SE]; S-112 87 Stockholm (SE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ARNERIC, Stephen, P.** [US/US]; 3498 Whistling Lane, Portage, MI 49024 (US). **ANDERSSON, Per-Olof** [SE/US]; 15 Dodgwood Drive, Whitehouse Station, NJ 08889 (US).

(74) Agents: **TANNERFELDT, Agneta et al.**; Pharmacia AB, Patent Department, S-112 87 Stockholm (SE).

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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF URINARY DISORDERS

(57) Abstract: The present invention concerns the field of urology. The invention provides a novel pharmaceutical composition, comprising a pharmaceutically effective combination of (i) a first compound selected from the group consisting of muscarinic receptor antagonists, 5 $\alpha$ -reductase inhibitors, and  $\alpha$ -adrenergic receptor antagonists, and precursors and pharmaceutically acceptable salts thereof, and (ii) a second compound selected from the group consisting of 5-HT<sub>4</sub> receptor agonists and antagonists, and precursors and pharmaceutically acceptable salts thereof, and optionally a pharmaceutically acceptable carrier or diluent therefor. There is also provided a method of therapeutical treatment of urinary disorder in a mammal, including man, comprising administering to said mammal, including man, in need of such treatment, a therapeutically effective amount of a composition according to the invention.

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Pharmaceutical compositions for the treatment of urinary disorders.

Technical field

The present invention is within the field of urology. More specifically, it is generally based on the use of a combination of certain agonists and/or  
5 antagonists for therapeutical treatment of urinary disorder.

Background of the invention

Urinary disorders and symptoms thereof include some  
10 or all of the following: urgency, frequency, incontinence, urine leakage, enuresis, dysuria, hesitancy, and difficulty of emptying bladder. In particular, urinary disorders include urinary incontinence, caused by e.g. unstable or overactive  
15 urinary bladder.

The term Lower Urinary Tract Symptoms (LUTS) describes a well-recognized medical condition. LUTS include some or all of the following: obstructive urinary symptoms, such as slow urination, dribbling at the end of  
20 a urination, inability to urinate and/or the need to strain to urinate at an acceptable rate, or irritative symptoms, such as frequency and/or urgency. These irritative symptoms may result from detrusor overactivity secondary to bladder outlet obstruction resulting from  
25 prostatic enlargement or proximal urethral smooth muscle hyperreactivity.

A substantial part (5-10%) of the adult population suffers from urinary incontinence, and the prevalence, particularly of so-called urge incontinence, increases  
30 with age. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. Urge incontinence in combination with stress incontinence (mixed incontinence) is frequently encountered by clinicians.

It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibers forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or overactive bladder has traditionally been based on muscarinic receptor antagonists.

The reason why the bladder muscle contracts inappropriately is unclear in many cases. For some people it may be due to a problem with the nerve signals that run from the brain to the bladder. Sometimes minor nerve damage is caused by surgery or childbearing. This muscle squeezes or contracts more often than normal and at inappropriate times. Instead of staying at rest as urine fills the bladder, the detrusor contracts while the bladder is filling with urine. This causes a person to feel a sudden and sometimes overwhelming urge to urinate even when the bladder is not full.

Another major urinary disorder is interstitial cystitis. Cystitis is an inflammation of the urinary bladder and associated structures. There is currently no universal effective treatment program. Symptoms from cystitis include urgency for urination, increased frequency of urination and suprapubic pain, usually relieved by voiding, arthritis, spastic colon, low grade fever and irritability. Mammals with cystitis can be significantly disabled and may require surgery. Cystitis can result from e.g. infection, trauma, allergy and malignancy.

US Patent 5,382,600 discloses 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol, also known as N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, with the generic name of tolterodine, as well as other substituted 3,3-diphenylpropylamines, as being useful to treat urinary incontinence. H Postlind et

al, Drug Metabolism and Disposition, 26(4): 289-293  
(1998) discloses that tolterodine is a muscarinic  
receptor antagonist. The active metabolites of  
tolterodine, as well as other substituted 3,3-  
5 diphenylpropylamines, are disclosed in US Patent  
5,559,269.

US Patent 4,377,584 discloses the use of  
finasteride, a 5 $\alpha$ -reductase inhibitor, for the treatment  
of benign prostatic hypertrophy.

10 US Patent 4,026,894 discloses the use of terazosin,  
an  $\alpha$ -adrenergic receptor antagonist, as an anti-  
hypertensive agent.  $\alpha$ -adrenergic receptor antagonists  
relax smooth muscle.

US Patent 5,990,114 discloses the use of certain  
15 5-HT<sub>1a</sub> receptor antagonists for the treatment of urinary  
incontinence.

Despite the above advances in the art, it is  
desirable to develop novel pharmaceutical compositions  
that further improve the quality of life for a large  
20 number of individuals.

#### Summary of the invention

For these and other purposes, it is an object of the  
present invention to provide a novel pharmaceutical  
25 composition for treating urinary disorder in a mammal,  
including man, which composition inhibits, or suppresses,  
unstable bladder contractions and diminishes problems  
associated with incomplete bladder emptying.

It is also an object of the present invention to  
30 provide a novel method of treating urinary disorder in a  
mammal, including man, which method effectively inhibits,  
or suppresses, unstable bladder contractions and  
diminishes problems associated with incomplete bladder  
emptying.

35 For these and other objects that will be evident  
from the following disclosure, the present invention  
provides a novel pharmaceutical composition, comprising a

pharmaceutically effective combination of  
(i) a first compound selected from the group consisting  
of muscarinic receptor antagonists, 5 $\alpha$ -reductase  
inhibitors, and  $\alpha$ -adrenergic receptor antagonists, and  
5 precursors and pharmaceutically acceptable salts thereof,  
and  
(ii) a second compound selected from the group consisting  
of 5-HT<sub>1a</sub> receptor agonists and antagonists, and  
precursors and pharmaceutically acceptable salts thereof,  
10 and optionally a pharmaceutically acceptable carrier or  
diluent therefor.

The invention is based on the insight that a  
combination of at least one compound selected from the  
group consisting of muscarinic receptor antagonists, 5 $\alpha$ -  
15 reductase inhibitors, and  $\alpha$ -adrenergic receptor  
antagonists, with a 5-HT<sub>1a</sub>-agonist or -antagonist produces  
a favorable simultaneous effect on bladder contractility  
and bladder storage, as will be described more below.  
The 5-HT<sub>1a</sub>-agonist could e.g. be an inverse agonist and  
20 the 5-HT<sub>1a</sub> -antagonist could be a neutral 5-HT<sub>1a</sub> receptor  
antagonist

In a preferred embodiment of the composition  
according to the invention, said first compound is a  
muscarinic receptor antagonist, or a precursor or a  
25 pharmaceutically acceptable salt thereof.

In a more preferred embodiment of the composition  
according to the invention, said muscarinic receptor  
antagonist is a substituted 3,3-diphenylpropylamine.  
Among substituted 3,3-diphenylpropylamines with  
30 muscarinic receptor antagonist activity are those  
referred to in the background of the invention.

In an even more preferred embodiment of the  
composition according to the invention, said substituted  
3,3-diphenylpropylamine is selected from the group  
35 consisting of tolterodine and hydroxytolterodine.  
Preferably, said substituted 3,3-diphenylpropylamine is  
tolterodine. In the most preferred embodiment of the

composition according to the invention, said first compound is tolterodine L-tartrate.

In another preferred embodiment of the composition according to the invention, said muscarinic receptor antagonist is selected from oxybutynin and active derivatives thereof. Among active derivatives thereof is its active metabolite N-desethyloxybutynin. Preferably, said muscarinic receptor antagonist is oxybutynin.

In yet another preferred embodiment of the composition according to the invention, said muscarinic receptor antagonist is selected from darifenacin and active derivatives thereof. Among active derivatives thereof is its active 3'-hydroxyl metabolite. Preferably, said muscarinic receptor antagonist is darifenacin.

In one preferred embodiment of the composition according to the invention, said first compound is present in an amount of from about 0.1 mg to about 100 mg.

In a preferred embodiment of the composition according to the invention, said second compound is a neutral 5-HT<sub>1a</sub> receptor antagonist.

In one preferred embodiment of the composition according to the invention, said second compound is present in an amount of from about 0.1 mg to about 1 g.

In another preferred embodiment of the composition according to the invention, said first compound and said second compound are maintained in the same delivery vehicle.

In yet another preferred embodiment of the composition according to the invention, said first compound and said second compound are maintained in different delivery vehicles.

In a preferred embodiment of the composition according to the invention, said composition is for treating urinary disorder in a mammal, especially man but also animals are included, e.g. pets like dogs and cats. In a more preferred embodiment of the composition

according to the invention, said disorder is selected from the group consisting of lower urinary tract symptoms, unstable or overactive urinary bladder, bladder outflow obstruction, urinary incontinence, particularly stress incontinence, and interstitial cystitis.

In another preferred embodiment of the composition according to the invention, said composition is for treating depression in said mammal, which depression is concomitant with said urinary disorder.

Furthermore, the present invention provides use of the composition according to the invention for the manufacture of a medicament for therapeutical treatment of urinary disorder in a mammal, including man. In a preferred embodiment of the use according to the invention, the medicament is for treatment of depression in said mammal, which depression is concomitant with said urinary disorder.

Furthermore, the present invention provides a method of therapeutical treatment of urinary disorder in a mammal, including man, comprising administering to said mammal, including man, in need of such treatment, a therapeutically effective amount of a composition according to the invention.

In a preferred embodiment of the method according to the invention, said disorder is selected from the group consisting of lower urinary tract symptoms, unstable or overactive urinary bladder, bladder outflow obstruction, urinary incontinence, particularly stress incontinence, and interstitial cystitis.

In another preferred embodiment of the method according to the invention, said method is also for treating depression in said mammal, which depression is concomitant with said urinary disorder.

In a preferred embodiment of the method according to the invention, said composition is administered rectally, intravaginally, topically, orally, sublingually, intranasally, transdermally or parenterally.

In another preferred embodiment of the method according to the invention, said first compound and said second compound of said composition are simultaneously administered.

5 In yet another preferred embodiment of the method according to the invention said first compound and said second compound of said composition are concomitantly administered.

Finally, the present invention provides a  
10 pharmaceutical kit for therapeutical treatment of urinary disorder in a mammal, including man, comprising  
(i) a first container comprising a first compound as described above  
(ii) a second container comprising a second compound as  
15 described above, and  
(iii) instructions for use of the kit.

#### Description of the invention

In describing the preferred embodiment, certain  
20 terminology will be utilized for the sake of clarity. Such terminology is intended to encompass the recited embodiments, as well as all technical equivalents that operate in a similar manner for a similar purpose to achieve a similar result. To the extent that any  
25 pharmaceutically active compound is disclosed or claimed, it is expressly intended to include all active metabolites produced in vivo, and, is expressly intended to include all enantiomers, isomers or tautomers where the compound is capable of being present in its  
30 enantiomeric, isomeric or tautomeric form.

The present invention provides a novel composition, which is a combination of  
at least one muscarinic receptor antagonist or 5 $\alpha$ -  
35 reductase inhibitor or  $\alpha$ -adrenergic receptor antagonist or norepinephrine and/or serotonin reuptake inhibitor



and

a 5-HT<sub>1a</sub> agonist or antagonist.

The inventive composition is useful for the treatment of urinary disorder.

- 5       A particularly preferred composition for the treatment of urinary disorder is a combination of an anti-muscarinic agent and a neutral 5-HT<sub>1a</sub>-antagonist.

10       According to the invention, it has now surprisingly and inventively been found that treatment with a combination of an anti-muscarinic agent and a neutral 5-HT<sub>1a</sub>-antagonist produces a simultaneous effect on bladder contractility and bladder storage.

15       Anti-muscarinic treatment acts on the effector organ by inhibiting the response to efferent impulses from the central nervous system. Thus, anti-muscarinic treatment inhibits unstable bladder contractions during the filling phase but also inhibits the contractions elicited during the elimination phase, especially at higher doses, 20       thereby resulting in a decrease in micturition pressure, eventually leading to the negative consequence of incomplete bladder emptying. This effect limits the possibilities of otherwise acceptable dosing of these agents. Furthermore, anti-muscarinic treatment leads to 25       side-effects outside of the urogenital systems, mainly due to blockade of muscarinic receptors in other tissues such as the salivary glands, the gut, and the CNS, leading to side effects such as dry mouth, constipation, and confusion, respectively. To some extent, these side 30       effects have been reduced by the introduction of newer anti-muscarinic agents such as tolterodine with selectivity for bladder smooth muscle. However, even bladder-selective anti-muscarinic agents will always be limited as a treatment of overactive bladder by their 35       effect on the micturition contraction described above.

      The effects of anti-muscarinic agents have been studied in a range of animal models and they have

consistently been shown to reduce the amplitude of voiding or micturition contraction without direct effects on bladder capacity. For these agents, the effects on bladder capacity have always been shown to be secondary .

5 to a significant decrease in micturition pressure.

No clinically available agents have any direct effect on the storage function of the bladder. However, it has now been realized that a combination of 5-HT<sub>1a</sub>-agonists or -antagonists, particularly neutral 5-HT<sub>1a</sub>-  
10 antagonists, and antimuscarinic agents or 5 $\alpha$ -reductase inhibitors or  $\alpha$ -adrenergic receptor antagonists or norepinephrine and/or serotonin reuptake inhibitors, particularly antimuscarinic agents, increases bladder capacity without negative consequences on bladder  
15 contractility.

Importantly, in models for the evaluation of the effects of an anti-muscarinic agent on bladder contractility, simultaneous administration of a neutral 5-HT-antagonist with an anti-muscarinic does not  
20 attenuate the effects of the anti-muscarinic agent on bladder contractility.

Furthermore, in models used for evaluation of the effects of neutral 5-HT<sub>1a</sub> antagonists on bladder capacity and inhibition of the micturition reflex, simultaneous  
25 administration of an anti-muscarinic agent with a neutral 5-HT<sub>1a</sub>-antagonist does not attenuate the effects of the 5-HT<sub>1a</sub>-antagonist on bladder capacity or its effect on the micturition reflex.

30 The muscarinic receptor antagonists, or antimuscarinic agents, useful in the pharmaceutical compositions of this invention include, but are not limited to, non-selective agents, bladder-selective agents and muscarinic M3 receptor-selective agents.  
35 Examples of muscarinic receptor antagonists include, but are not limited to, tolterodine and active metabolites thereof, such as hydroxytolterodine, YM905, propiverine,

oxybutynin, trospium, propantheline, darifenacin, temiverine, and ipratropium, as well as pharmaceutically acceptable salts thereof. YM905 is butanedioic acid, compd. with (1S)-(3R)-1-azabicyclo[2.2.2]oct-3-yl 3,4-  
5 dihydro-1-phenyl-2(1H)-isoquinolinecarboxylate (1:1) (9CI). Propiverine is 1-methyl-4-piperidyl .alpha.,.alpha.-diphenyl-.alpha.-(n-propoxy)acetate and is disclosed in East German Patent 106,643 and in CAS 82-155841s (1975). Oxybutynin is 4-(diethylamino)-2-  
10 butynylalphaphenylcyclohexaneglycolate and is disclosed in UK Patent 940,540. Trospium is 3alpha-hydroxyspiro[1alphaH,5alphaH-nortropane-8,1'pyrrolidinium]chloride benzilate and is disclosed in US Patent 3,480,623. Darifenacin is (S)-2-{1-[2-(2,3-  
15 dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenyl-acetamide, and is disclosed in US Patent 5,096,890. Temiverine is benzeneacetic acid, .alpha.-cyclohexyl-.alpha.-hydroxy-, 4-(diethylamino)-1,1-dimethyl-2-butynyl ester and is disclosed in US Patent  
20 5,036,098. Ipratropium is 8-isopropylnoratropine methobromide and is disclosed in US Patent 3,505,337.

Preferred muscarinic receptor antagonists may be selected from substituted 3,3-diphenylpropylamines (such as those disclosed in US Patent 5,382,600) with  
25 antimuscarinic activity, as well as pharmaceutically acceptable salts thereof. Preferred muscarinic receptor antagonists include, but are not limited to tolterodine and hydroxytolterodine, oxybutynin and active derivatives thereof, such as N-desethyloxybutynin, and darifenacin  
30 and active derivatives thereof, such as its 3'-hydroxyl metabolite, as well as pharmaceutically acceptable salts thereof.

The 5 $\alpha$ -reductase inhibitors useful in the pharmaceutical compositions of this invention include,  
35 but are not limited to, finasteride (US Patent 4,377,584), dutasteride (US Patent 5,565,467), epristeride (US Patent 5,017,568), and turosteride (US

Patent 5,155,107), as well as pharmaceutically acceptable salts thereof.

The  $\alpha$ -adrenergic receptor antagonists useful in the pharmaceutical compositions of this invention include, but are not limited to, terazosin (US Patent 4,026,894), doxazosin (US Patent 4,188,390), prazosin (US Patent 3,511,836), bunazosin (US Patent 3,920,636), indoramin (US Patent 3,527,761), alfuzosin (US Patent 4,315,007), abanoquil (US Patent 4,686,228), naftopidil (US Patent 3,997,666), phentolamine, tamsulosin (US Patent 4,703,063), trazodone, dapiprazole, phenoxybenzamine, idazoxan (US Patent 4,818,764), efaroxan (US Patent 4,411,908), yohimbine, dibenzamine, trimazosin, tolazoline, corynthanine, rauwolscine, tamsulosin, and piperoxan, as well as pharmaceutically acceptable salts thereof.

The norepinephrine and/or serotonin reuptake inhibitors useful in the pharmaceutical compositions of this invention include, but are not limited to, duloxetine (US Patent 4,956,388), reboxetine, [S,S]-reboxetine succinate salt and the racemates of reboxetine and sertraline (Zoloft).

The selection of the dosage of the first compound is that which can provide relief to the patient. As is well known, the dosage and administrative regimen (i.e., one, two, three or more administrations per day) of this compound depends on several factors such as the potency of the selected specific compound, the mode of administration, the age and weight of the patient, the severity of the condition to be treated, and the like. This is considered to be within the skill of the artisan, and one can review the existing literature on the components to determine optimal dosing.

When the first compound is an antimuscarinic agent, it is preferred that the average adult daily dosage of

the first compound is from about 0.05 mg to about 5 mg per kilogram of body weight, administered in one or more doses, e.g. containing from about 0.05 mg to about 250 mg each.

- 5        When the first compound is a 5 $\alpha$ -reductase inhibitor, it is preferred that the first compound is present in an amount ranging from about 2 mg to about 20 mg, preferably about 5 mg per dose.

- 10        When the first compound is an  $\alpha$ -adrenergic receptor antagonist, it is preferred that the first compound is present in an amount ranging from about 1 mg to about 25 mg, and preferably about 10 mg per dose.

- 15        The 5-HT<sub>1a</sub> receptor agonists and antagonists useful in the pharmaceutical compositions of this invention include, but are not limited to, compounds that act on the central nervous system by binding to 5-HT receptors of the 5-HT<sub>1a</sub> subtype. Non-limiting examples of 5-HT<sub>1a</sub> receptor antagonists are WAY-100,635, i.e. cyclohexanecarboxamide, N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl-, trihydrochloride, 20        robalzotan, i.e. (3R)-3-(dicyclobutylamino)-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide, and LY426965, i.e. [(2S)-(+)-1-cyclohexyl-4-[4-(2-methoxyphenyl)-1-piperazinyl]2-methyl-2-phenyl-1-butanone monohydrochloride]. In general, the compounds selectively 25        bind to receptors of the 5-HT<sub>1a</sub> subtype to a much greater extent than they bind to other receptors, such as  $\alpha_1$  and D<sub>2</sub> receptors. Moreover, they exhibit activity as 5-HT<sub>1a</sub>-agonists or -antagonists in pharmacological testing. The 30        5-HT<sub>1a</sub> receptor agonists and antagonists of the invention can be used for the treatment of CNS disorders, such as anxiety in mammals, particularly humans. They may also be used as antidepressants, hypotensives, as agents for regulating the sleep/wake cycle, feeding behavior and/or 35        sexual function, for treating cognition disorders, and for treating neuromuscular dysfunction of the lower

urinary tract, particularly those involving micturition (urination), such as dysuria, incontinence, and enuresis.

A neutral antagonist is a compound that binds to a receptor, is devoid of intrinsic activity at the  
5 receptor, but blocks the receptor-mediated functional activity elicited by an agonist. In this respect, an agonist is defined as a compound that binds to a receptor and activates a receptor-mediated functional response such as, but not limited to, 5-HT<sub>1a</sub>-mediated inhibition of  
10 adenylyl cyclase activity or activation of potassium channels.

The dosage and administrative regimen (i.e., one, two, three or more administrations per day) of the second compound depends on the factors referred to in connection  
15 with the dosage selection of the first compound. The average adult daily dosage of the second compound is from about 1 µg to about 10 mg per kilogram of body weight, administered in one or more doses, e.g. containing from about 50 µg to about 1 g each. Pediatric dosages may be  
20 less.

Examples of pharmaceutically acceptable salts for use in the composition according to the invention include, but are not limited to, acetate, benzoate,  
25 hydroxybutyrate, bisulfate, bisulfite, bromide, butyne-1,4-dioate, carpoate, chloride, chlorobenzoate, citrate, dihydrogenphosphate, dinitrobenzoate, fumarate, glycollate, heptanoate, hexyne-1,6-dioate, hydroxybenzoate, iodide, lactate, maleate, malonate,  
30 mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, oxalate, phenylbutyrate, phenylproionate, phosphate, phthalate, phylacetate, propanesulfonate, propiolate,  
35 propionate, pyrophosphate, pyrosulfate, sebacate, suberate, succinate, sulfate, sulfite, sulfonate, tartrate, xylenesulfonate, and the like.

Compositions of the present invention can conveniently be administered in a pharmaceutical composition containing the active compounds in combination with a suitable excipient. Such  
5 pharmaceutical compositions can be prepared by methods and contain excipients which are well known in the art. A generally recognized compendium of such methods and ingredients is Remington's Pharmaceutical Sciences by E.W. Martin (Mark Publ. Co., 15th Ed., 1975). To the  
10 extent necessary for completion, this reference is hereby incorporated by reference. The compositions of the present invention can be administered parenterally (for example, by intravenous, intraperitoneal, subcutaneous or intramuscular injection), topically, orally,  
15 sublingually, transdermally, intranasally, intravaginally, or rectally, with oral administration being particularly preferred.

For oral therapeutic administration, the inventive composition may be combined with one or more excipients  
20 and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums, foods and the like. Such compositions and preparations preferably contain at least 0.1% of active compounds. The percentage of the  
25 compositions and preparations may, of course, be varied and may conveniently be between about 0.1 to about 100% of the weight of a given unit dosage form. The amount of active compounds in such therapeutically useful compositions is such that effective dosage levels will be  
30 obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients  
such as dicalcium phosphate; a disintegrating agent such  
35 as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or

a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. The above listing is merely representative, and one skilled in the art could envision other binders, excipients, sweetening agents and the like. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active components may be incorporated into sustained-release preparations and devices including, but not limited to, those relying on osmotic pressures to obtain a desired release profile. Once daily formulations for each of the active components are specifically included.

The inventive composition, containing the two, or more, active compounds, may be administered in the same physical form or concomitantly according to the above-described dosages and in the above-described delivery vehicles. The dosages for each active compound can be measured separately and can be given as a single combined dose or given separately. They may be given at the same or at different times as long as both actives are in the patient at one time over a 24-hour period. Concomitant or concurrent administration means that the patient takes one drug within about 5 minutes of taking the other drug.

The present invention also provides a pharmaceutical kit for therapeutical treatment of urinary disorder in a mammal, including man. In analogy with the composition,



the kit comprises a first container comprising a first compound as described above, a second container comprising a second compound as described above, and instructions for use of the kit.

5

"Pharmaceutically acceptable" refers to those properties and/or substances that are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

The inventive composition is to be used in the treatment of urinary disorders. In particular, the composition is useful for treating LUTS or incontinence of any type, e.g. stress incontinence, genuine stress incontinence, and mixed incontinence. Stress urinary incontinence is a symptom describing involuntary loss of urine on carrying out any activity that raises intra-abdominal pressure such as coughing or sneezing. Stress incontinence is also a clinical sign, that is the observation by a care giver of a jet of urine escaping from the urethral meatus (opening) when the patient coughs or strains. Genuine Stress Incontinence (urge incontinence) is the pathological diagnosis of an incompetent urethral sphincter as diagnosed by Urodynamic testing. Mixed incontinence is stress incontinence in combination with urge incontinence. The latter is a part of the symptom complex of the Overactive Bladder. Retention may be due to outflow obstruction (e.g., high urethral pressure), poor detrusor (bladder muscle) contractility or lack of coordination between detrusor contraction and urethral relaxation. The inventive drug combination can be used in connection with stress incontinence, urge incontinence or mixed incontinence.

The composition according to the invention is also to be used in the treatment of interstitial cystitis.

In a situation where anti-muscarinic treatment of a urinary disorder is limited by an increase in residual  
5 urine, treatment can be augmented by the addition of a neutral 5-HT<sub>1a</sub> antagonist. This situation is especially likely to occur in patients with overactive bladder secondary to bladder outflow obstruction, e.g. due to prostate enlargement.

10 In other cases, anti-muscarinic treatment might be limited by intolerable side effects, such as dry mouth. In such a case, the anti-muscarinic dose might be reduced but efficacy maintained by the addition of a neutral 5-HT<sub>1a</sub> antagonist. This combination allows the use of anti-  
15 muscarinic agents that are not selective for the bladder in a situation where these agents are preferred over other, more bladder selective, agents.

In another situation, treatment with a neutral 5-HT<sub>1a</sub> antagonist might be limited due to absence of an effect  
20 on bladder contractility. In such a case, addition of an anti-muscarinic agent brings additional efficacy. Such a situation might be patients with bladder hyperreflexia, a condition known to be associated with increased reflex bladder contractions.

25 In yet another situation, the effectiveness of a neutral 5-HT<sub>1a</sub> antagonist might be limited by side effects. In such a case, adjustment of the dose of the 5-HT antagonist, and thereby its effectiveness can be compensated for by the addition of an anti-muscarinic  
30 agent.

The novel composition is considered to provide rapid relief to those suffering from the above diseases or disorders with a minimal amount of deleterious side effects.

35 The invention is described in greater detail by the following non-limiting examples.

ExamplesExample 1

A pharmaceutical composition is prepared by  
5 combining tolterodine with a neutral 5-HT<sub>1a</sub> receptor  
antagonist in a pharmaceutically acceptable carrier. The  
composition contains between about 0.05 mg to about 4 mg  
of tolterodine per kilogram of patient body weight (for  
example, 3 mg to 240 mg tolterodine for a person weighing  
10 60 kg) and between about 0.01 mg to about 1 mg of neutral  
5-HT<sub>1a</sub> receptor antagonist per kilogram of patient body  
weight. The composition is administered to a patient for  
the treatment of incontinence, and particularly stress  
incontinence, urge incontinence or mixed incontinence.

15

Example 2

A first pharmaceutical composition is prepared by  
combining a neutral 5-HT<sub>1a</sub> receptor antagonist in a  
pharmaceutically acceptable carrier such that it can  
20 deliver between about 0.5 mg to about 50 mg on a daily  
basis. A second pharmaceutical composition is prepared by  
combining tolterodine in a pharmaceutically acceptable  
carrier such that it can deliver between about 0.05 mg to  
about 4 mg of tolterodine per kilogram of patient body  
25 weight on a daily basis.

The first composition is administered to a patient  
suffering from one or more forms of incontinence once,  
twice, three times, four times or six times daily such  
that the daily dosage is between about 0.5 mg to about 50  
30 mg. The second composition is administered to the same  
patient at the same time as the administration of the  
first composition or any time within 24 hours of the  
administration of the first composition once, twice,  
three times, four times or six times daily such that the  
35 daily dosage is between about 0.05 mg to about 4 mg of  
tolterodine per kilogram of patient body weight.  
Alternatively, the second composition could first be

administered, followed by the administration of the first composition as disclosed at the same time, or within 24 hours thereof.

5    Example 3

          A pharmaceutical composition is prepared by combining a 5 $\alpha$ -reductase inhibitor with a neutral 5-HT<sub>1a</sub> receptor antagonist in a pharmaceutically acceptable carrier. The composition contains between about 2 mg to  
10    about 20 mg of 5 $\alpha$ -reductase inhibitor and between about 0.5 mg to about 50 mg of neutral 5-HT<sub>1a</sub> receptor antagonist. The composition is administered to a patient for the treatment of urinary disorder.

15    Example 4

          A pharmaceutical composition is prepared by combining an  $\alpha$ -adrenergic receptor antagonist with a neutral 5-HT<sub>1a</sub> receptor antagonist in a pharmaceutically acceptable carrier. The composition contains between  
20    about 1 mg to about 25 mg of  $\alpha$ -adrenergic receptor antagonist and between about 0.5 mg to about 50 mg of neutral 5-HT<sub>1a</sub> receptor antagonist. The composition is administered to a patient for the treatment of urinary disorder.

25

          Having described the invention in detail and by reference to the preferred embodiments thereof, it will be apparent that modifications and variations are possible without departing from the scope of the appended  
30    claims.

CLAIMS

1. A pharmaceutical composition comprising a pharmaceutically effective combination of
- 5 (i) a first compound selected from the group consisting of muscarinic receptor antagonists, 5 $\alpha$ -reductase inhibitors, and  $\alpha$ -adrenergic receptor antagonists, and precursors and pharmaceutically acceptable salts thereof, and
- 10 (ii) a second compound selected from the group consisting of 5-HT<sub>1a</sub> receptor agonists and antagonists, and precursors and pharmaceutically acceptable salts thereof, and optionally a pharmaceutically acceptable carrier or diluent therefor.
- 15 2. A pharmaceutical composition according to claim 1, wherein said first compound is a muscarinic receptor antagonist, or a precursor or a pharmaceutically acceptable salt thereof.
3. A composition according to claim 2, wherein said
- 20 muscarinic receptor antagonist is a substituted 3,3-diphenylpropylamine.
4. A composition according to claim 3, wherein said substituted 3,3-diphenylpropylamine is selected from the group consisting of tolterodine and hydroxytolterodine.
- 25 5. A composition according to claim 4, wherein said substituted 3,3-diphenylpropylamine is tolterodine.
6. A composition according to claim 5, wherein said first compound is tolterodine L-tartrate.
7. A composition according to claim 2, wherein said
- 30 muscarinic receptor antagonist is selected from oxybutynin and active derivatives thereof, such as N-desethyloxybutynin.
8. A composition according to claim 7, wherein said muscarinic receptor antagonist is oxybutynin.
- 35 9. A composition according to claim 2, wherein said muscarinic receptor antagonist is selected from

darifenacin and active derivatives thereof, such as its 3'-hydroxyl metabolite.

10. A composition according to claim 9, wherein said muscarinic receptor antagonist is darifenacin.

5        11. A composition according to any one of claims 1-10, wherein said first compound is present in an amount of from about 0.1 mg to about 100 mg.

10        12. A composition according to any one of claims 1-11, wherein said second compound is a neutral 5-HT<sub>1A</sub> receptor antagonist.

13. A composition according to any one of claims 1-12, wherein said second compound is present in an amount of from about 0.1 mg to about 1 g.

15        14. A composition according to any one of claims 1-13, wherein said first compound and said second compound are maintained in the same delivery vehicle.

15. A composition according to any one of claims 1-13, wherein said first compound and said second compound are maintained in different delivery vehicles.

20        16. A composition according to any one of claims 1-15, which is for treating urinary disorder in a mammal, including man.

17. A composition according to claim 16, wherein said disorder is lower urinary tract symptoms.

25        18. A composition according to claim 16, wherein said disorder is unstable or overactive urinary bladder.

19. A composition according to claim 16, wherein said disorder is bladder outflow obstruction.

30        20. A composition according to claim 16, wherein said disorder is urinary incontinence.

21. A composition according to claim 20, wherein said disorder is stress incontinence.

22. A composition according to claim 16, wherein said disorder is interstitial cystitis.

35        23. A composition according to any one of claims 16-22, which is for treating depression in said mammal,

which depression is concomitant with said urinary disorder.

24. Use of a pharmaceutical composition according to any one of claims 1-15 for the manufacture of a medicament for therapeutical treatment of urinary disorder in a mammal, including man.

25. Use of a pharmaceutical composition according to claim 24, wherein said disorder is lower urinary tract symptoms.

26. Use of a pharmaceutical composition according to claim 24, wherein said disorder is unstable or overactive urinary bladder.

27. Use of a pharmaceutical composition according to claim 24, wherein said disorder is bladder outflow obstruction.

28. Use of a pharmaceutical composition according to claim 24, wherein said disorder is urinary incontinence.

29. Use of a pharmaceutical composition according to claim 28, wherein said disorder is stress incontinence.

30. Use of a pharmaceutical composition according to claim 24, wherein said disorder is interstitial cystitis.

31. Use of a pharmaceutical composition according to any one of claims 24-30, wherein the medicament is for treatment of depression in said mammal, which depression is concomitant with said urinary disorder.

32. A method of therapeutical treatment of urinary disorder in a mammal, including man, comprising administering to said mammal, including man, in need of such treatment, a therapeutically effective amount of a composition according to any one of claims 1-15.

33. A method of therapeutical treatment according to claim 32, wherein said disorder is lower urinary tract symptoms.

34. A method of therapeutical treatment according to claim 32, wherein said disorder is unstable or overactive urinary bladder.

35. A method of therapeutical treatment according to claim 32, wherein said disorder is bladder outflow obstruction.

36. A method of therapeutical treatment according to claim 32, wherein said disorder is urinary incontinence.

37. A method of therapeutical treatment according to claim 36, wherein said disorder is stress incontinence.

38. A method of therapeutical treatment according to claim 32, wherein said disorder is interstitial cystitis.

39. A method of therapeutical treatment according to any one of claims 32-38, which is also for treatment of depression in said mammal, which depression is concomitant with said urinary disorder.

40. A method of therapeutical treatment according to any one of claims 32-39, wherein said composition is administered rectally, intravaginally, topically, orally, sublingually, intranasally, transdermally or parenterally.

41. A method of therapeutical treatment according to any one of claims 32-40, wherein said first compound and said second compound of said composition are simultaneously administered.

42. A method of therapeutical treatment according to any one of claims 32-40, wherein said first compound and said second compound of said composition are concomitantly administered.

43. A pharmaceutical kit for therapeutical treatment of urinary disorder in a mammal, including man, comprising

- (i) a first container comprising a first compound according to any one of claims 1-10,
- (ii) a second container comprising a second compound according to claim 1 or 12, and optionally
- (iii) instructions for use of the kit.



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01748

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/137, A61K 31/165, A61K 31/216, A61K 31/343, A61K 31/4025,  
A61P 13/02, A61P 13/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, EPO, INTERNAL, MEDLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 0121167 A1 (MERCK & CO., INC.), 29 March 2001 (29.03.01), (5alpha-reductase inhibitors, alpha-adrenergic receptor antagonists and muscarinic receptor antagonists are known for the treatment of Lower Urinary Tract Symptoms (LUTS).	1-43
Y	See page 1, lines 6-16 and 21-23; page 2, line 7 - page 5, line 2.) --	
Y	UROLOGY, Vol. 56, Suppl. 6A, 2000, Roger R. Dmochowski et al: "Advancements in pharmacologic management of the overactive bladder", page 41 - page 49 --	1-43

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

9 December 2002

Date of mailing of the international search report

18-12-2002

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No. +46 8 666 02 86

Authorized officer

Per Renström/EÖ  
Telephone No. +46 8 782 25 00

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01748

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Life Sciences, Vol. 64, No. 6/7, 1999, Robert M. Walles et al: "Muscarinic antagonists in development for disorders of smooth muscle function", page 395 - page 401  --	1-43
Y	EP 0930298 A1 (BANYU PHARMACEUTICAL CO., LTD.), 21 July 1999 (21.07.99), (Muscarinic (M3) antagonists for the treatment of urinary disorders like urinary incontinence. See abstract; page 3, lines 25-33; page 4, lines 4-10; examples; claims.)  --	1-43
Y	WO 9921563 A1 (MERCK & CO., INC.), 6 May 1999 (06.05.99), (Use of a 5alpha-reductase inhibitor (e.g. finasteride) for the treatment of urinary retention. See page 1, lines 20-25; page 3, line 11 - page 4, line 4; examples; claims.)  --	1-43
Y	WO 0129022 A1 (RECORDATI INDUSTRIA CHIMICA E FARMACEUTICA SPA), 26 April 2001 (26.04.01), (Alpha-1 adrenoceptor antagonists for treating lower urinary tract symptoms such as contractions of urethra and incontinence. See page 1-9.)  --	1-43
Y	WO 9605817 A1 (MEDINNOVA SF), 29 February 1996 (29.02.96), (Partial 5-HT1A agonists(e.g. azapirone, ipsapirone, gepirone and tandospirone) in the treatment of urinary incontinence, urinary retention and urethral	1-43
Y	resistance. Example with buspirone. See pages 4-7; pages 13-15, examples 6-8; table 1 on page 16; claims.)  --	

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01748

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 9731637 A1 (RECORDATI INDUSTRIA CHIMICA E FARMACEUTICA S.P.A. ET AL), 4 Sept 1997 (04.09.97), (Use of 5-HT1A receptor antagonists for the treatment of urinary incontinence, dysuria and enuresis.)  -- -----	1-43

# INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/SE02/01748**

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **32-42**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see extra sheet**
2. ☒ Claims Nos.: **1-43**  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
**see extra sheet**
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

**Box I.1**

Claims 32-42 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

**Box I.2**

The present claims 1-43 relate to compounds defined by reference to desirable properties, namely that they should be muscarinic receptor antagonists, 5 $\alpha$ -reductase inhibitors,  $\alpha$ -adrenergic receptor antagonists or 5-HT<sub>1A</sub> receptor agonists or antagonists. The claims cover compositions, and uses of compositions, involving all compounds having these properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

Independent of the above reasoning, the claims 1-43 also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to results to be achieved. This lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Specifically, the terms "muscarinic receptor antagonists", "5 $\alpha$ -reductase inhibitors", " $\alpha$ -adrenergic receptor antagonists" and "5-HT<sub>1A</sub> receptor agonists or antagonists" apparently relate to a very large amount of different compounds, which do not necessarily have to be defined with their respective receptor activities, thus rendering it impossible to perform a complete search.

The search has been carried out for the compounds mentioned in the present claims 3-10 in combination with the compounds mentioned in the description.

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

28/10/02

International application No.

PCT/SE 02/01748

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
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				IT MI960378 A,U	28/08/97
				JP 2001511763 T	14/08/01
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